A STUDY OF N-ALKYLATED CYCLOHEXEN-2-YLAMINES AND SOME RELATED HETEROCYCLIC DERIVATIVES

by

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PREFACE

The subject matter of this dissertation is presented in two sections for clarity. The cyclohexenylamines represent mainly syntheses, while the piperazines relate to exploratory techniques and attempts to synthesize a particular compound. The preparation of individual compounds is presented in detailed form so that future investigators may easily duplicate the work.

The manner of listing technical works is the customary one used by journals of the American Chemical Society. The abbreviations of journals are those adopted as official by Chemical Abstracts.

All temperatures are reported in degrees centigrade, and the centigrade symbol is omitted. All melting points and boiling points are corrected and were determined with thermometers calibrated against a set of thermometers corrected by the Bureau of Standards.

All yields of cyclohexenylamines are based upon the 3-bromocyclohexene used.

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CHAPTER I

INTRODUCTION

Certain derivatives of 1-phenylpiperazine have shown evidence of being useful in the field of medicine, particularly 1-phenyl-4-(2-hydroxyethyl)-piperazine and 1-phenyl-4-(2-hydroxy-3-methoxypropyl)-piperazine.[1,2] About five years ago 2,5-dimethylpiperazine and 2,6-dimethylpiperazine became available commercially, and it was felt that derivatives similar to those of piperazine would be of interest. With this in mind, 1-(2-hydroxyethyl)-2,5-dimethylpiperazine was prepared, and a phenyl group was substituted on the 4-position.

Considering the structure of cyclohexenylamine and its N-alkylated derivatives, it appeared favorable, from a theoretical point of view, to be a starting material for the synthesis of phenyl substituted amines. The literature lists examples of the disproportionation of cyclohexene to cyclohexane and benzene,[3] the catalytic dehydrogenation of cyclohexene to benzene,[4] the dehydrogenation of the cyclohexene ring with sulfur and selenium,[5] the stepwise dehydrohalogenation of brominated cyclohexene to benzene,[6] and the cleavage of various

groups from substituted cyclohexenes to form benzenes.[7] The idea of substituting a cyclohexenyl group on the 4-position of 1-(2-hydroxyethyl)-2,5-dimethylpiperazine and dehydrogenating or disproportionating to the phenyl group was conceived. This was unsuccessful, but the study of this compound indicated a great lack of information on the series of cyclohexenyl amines.

The literature lists only five compounds of the series $C_6H_9NR_1R_2$ in which R can be hydrogen, alkyl, aryl, or cyclic. Those listed include cyclohexen-2-ylamine,[8] N,N-dimethylcyclohexen-2-ylamine,[8] N,N-diethylcyclohexen-2-ylamine,[9] N-cyclohexen-2-ylpiperidine,[10,11] and N-phenylcyclohexen-2-ylamine.[12]

The synthesis of the simpler members of this series was necessary to help understand the more complicated piperazine compounds. The reactions of N,N-diethylcyclohexen-2-ylamine were of particular interest in this respect, since the pair of two member carbon chains closely approximated the basic structure of the piperazine compound.

This dissertation describes the preparation of a number of derivatives of cyclohexen-2-ylamine and various compounds of 2,5-dimethylpiperazine prepared as derivatives and intermediates.

The physical constants of these compounds, including boiling points, refractive indexes, and infrared absorption bands are presented. Derivatives for characterization of certain of these amines are listed with the parent compound.

CHAPTER II

A SURVEY OF THE PROBLEM

Review of the Literature

Following the establishment of piperazine as a compound in 1853, the chemistry of the family of substituted-piperazines was developed. C-Substituted piperazines are not as well known as piperazine itself. The methods by which any substituent may be placed at a given position on the piperazine ring are limited. 2,5- and 2,6-dimethylpiperazine were received with great interest when they were introduced commercially in 1949. Since that time the purity of the compounds has been improved, and individual geometrical isomers have become available. After the completion of this experimental work, Wyandotte Chemical Company announced the availability of cis and trans 2,5-dimethylpiperazine.

From a theoretical point of view, 2,5-dimethylpiperazine has been of interest for some time. The two stable geometrical isomers were separated by Stoer and were labeled alpha and beta 2,5-dimethylpiperazine in 1893-97.[13, 14] Pope and Read identified the trans

isomer in 1912-1914,[15, 16] while the dl-cis isomer was resolved via the d-hydroxymethylenecamphor derivative.[17] Interest then lagged until Carbide and Carbon Chemicals Company introduced the dimethylpiperazines. Since the commercial introduction, articles describing derivatives, usually unsymetrically substituted, of 2,5-dimethylpiperazine have appeared from time to time.[18-20] They usually were prepared for clinical testing because many piperazines show physiological activity.

Initially, the synthesis of 1-phenyl-4-(2-hydroxyethyl)-2,5-dimethylpiperazine was desired. 4-(2-Hydroxyethyl)-2,5-dimethylpiperazine was prepared by the method of Adelson and Pollard,[21] modified slightly to meet the conditions imposed by the physical properties of 2,5-dimethylpiperazine. Substitution of a phenyl group onto an amine is difficult, but it has been accomplished in certain specific cases. The addition of p-nitrobromobenzene to amines was accomplished by refluxing the alcoholic solution of the reactants or by melting the reactants together in a stoppered carbonated drink bottle.[22] The nitro group could then be reduced to the amine and either substituted or diazotized, the diazotized amine being either treated to remove the nitrogen to form the phenyl derivative or treated to substitute halogen

or nitrile for the nitrogen. The addition of p-chlorobenzoic acid can be accomplished by refluxing a mixture of the amine with p-chlorobenzoic acid, copper powder, and xylene.[23] Heating iodobenzene, the amine and copper powder for a number of hours will also cause substitution.[24] It was also believed that there was a good possibility of substituting a cyclohexene ring in the 1-position and dehydrogenating it to the phenyl group.[3-7] Cyclohexenyl amines with the amine group on the ring have been prepared in a number of ways. Mannich and Davidsen prepared cyclohexen-1-yl-piperidine from cyclohexanone and piperidine.[3] C. F. H. Allen, Alan Bell, and J. W. Gates prepared 1-nitro-2-phenyl-4-cyclohexene from butadiene and beta-nitrostyrene via the Diels-Alder reaction.[37] This, in turn, was reduced to the amine with hydrogen and Raney nickel. D. V. Nightingale and V. Tweedie prepared a number of phenyl derivatives in this manner.[38] J. Gutman prepared N,N-5-trimethylcyclohexen-2-ylamine and N,N-2-trimethylcyclohexen-2-ylamine from 1-methyl-3,4-dibromocyclohexane and 1-methyl-1,2-dibromocyclohexane treated with dimethylamine.[39, 40] Max Mousseron prepared several alkylated cyclohexenylamines from the 2-alkyl-1-amino-2-cyclohexanols by dehydration with phosphorous pentachloride.[41] Mousseron and Nanon prepared N,N-diethylcyclohexen-2-

ylamine,[9] Hofmann and Damm prepared both cyclohexen-2-ylamine and N,N-dimethylcyclohexen-2-ylamine,[8] and Arbuzov and Mastryurova prepared N-phenyl-cyclohexen-2-ylamine by reacting the appropriate amine with 3-bromocyclohexene prepared by means of the Wohl-Ziegler reaction.[25-28]

With the exception of the Wohl-Ziegler and the Diels-Alder reactions, the position of the double bond is in doubt since the part which is eliminated may be removed in either of two directions. These reactions require proof of structure. The Diels-Alder reaction provides only ring substituted derivatives, therefore, the Wohl-Ziegler reaction was chosen for the preparation of cyclohexenylamines of known structure. This reaction is reviewed by C. Djerassi in Chemical Reviews.[25] Ziegler et al. found that N-bromosuccinimide brominated methylene groups in preference to methyl groups and would not react with tertiary hydrogens.[26] They also found that cyclohexene was brominated in the 3-position exclusively and in high yields. Mousseron et al. investigated the effect of substituents on the cyclohexene ring and the position of the bromine substitution.[27] They found that 1-alkyl-1-cyclohexenes brominated in the 6-position, while the 1-chloro brominated in the 3-position.

Table 1 is extracted from this reference.

Various solvents, including carbon tetrachloride, benzene, petroleum ether or heptane, ethanol, or chloroform can be used in this reaction. Carbon tetrachloride is the usual solvent because the N-bromosuccinimide sinks while the succinimide formed floats, thus giving an indication of the progress of the reaction. Benzoyl peroxide is used as a catalyst.

It was felt that the simpler members of the cyclohexenylamine series should be studied in order to obtain a better idea of the problem. Very little information exists even on the simple members of this series. The amine itself, N,N-dimethyl-, N,N-diethyl-, phenyl-, and the N-cyclohexenylpiperidine are the only ones recorded that do not have ring substitution.

A number of these amines was prepared to elucidate this series and to provide physical constants and infrared spectra for comparisons in this study. From literature values already available, a comparison of cyclohexenylamines, anilines, and cyclohexylamines is made.[29-36]

Discussion

The problem resolves itself into the preparation of 1-(2-hydroxyethyl)-2,5-dimethylpiperazine, attempts to substitute a phenyl group in the 4-position by several

TABLE I

THE POSITION TAKEN BY THE BROMINE ATOM INTRODUCED INTO VARIOUS SUBSTITUTED CYCLOHEXENES BY N-BROMOSUCCINIMIDE

Reactant	Product
1-Methyl-1-cyclohexene	6-Bromo-1-methyl-1-cyclohexene
1-Methyl-2-cyclohexene	4-Bromo-1-methyl-2-cyclohexene
1-Methyl-3-cyclohexene	5-Bromo-1-methyl-3-cyclohexene
1-Ethyl-1-cyclohexene	6-Bromo-1-ethyl-1-cyclohexene
1,3-Dimethyl-3-cyclohexene	2-Bromo-1,3-dimethylcyclohexene
1-Chloro-1-cyclohexene	3-Bromo-1-chloro-1-cyclohexene
3-Bromocyclohexene	3,6-Dibromocyclohexene

methods, and the preparation and correlation of the physical properties of the simpler members of the cyclohexenylamine family. This was done to aid in the understanding of the reactions of the more complicated substituted piperazine derivatives.

The method used to prepare the cyclohexenylamine derivatives yields only one isomer which simplifies analysis via infrared spectra. The preparation of characterization derivatives has been made when possible. This step proved to be very difficult with this series because only the simplest tertiary amines yielded methiodides or picrates, and the secondary amines yielded oils in the lower members of the series and no product with the higher members of the series. The methiodide, picrate, phosphate, tartrate, 3,5-dinitrobenzoic acid salt, hydrochloride, hydrobromide, addition of HCl and HBr to the double bond, dibromination of the double bond, salicylic acid salt, and phthalic acid salt derivatives of the tertiary amines were attempted with success in some cases and failure in others. The phenylthiourea, benzenesulfonamide, and many of the derivatives listed above were used with the secondary amines.

CHAPTER III

SYNTHESIS AND PROPERTIES OF THE CYCLOHEXENYLAMINES

Experimental Work

The experimental part of this work, while closely related, is divided into two parts for purposes of clarity. The cyclohexenylamines represent mainly syntheses, while the piperazines relate to exploratory techniques and synthesis of a particular compound.

The cyclohexenylamines may be prepared either from the amine and a cyclohexene halide or from cyclohexenylamine via alkylation. The preparation of 3-bromocyclohexene is straightforward and furnishes high yields of product. Cyclohexene is available commercially, as is N-bromosuccinimide, a convenient brominating agent. The reaction is clean-cut, producing only the 3-bromo isomer. The halide, in addition to being convenient to make, is also very reactive with the amines used. 3-Bromocyclohexene can be made by other methods, such as the addition of hydrogen bromide to 1,3-cyclohexadiene with the hydrogen bromide adding 1,4- or by the treatment of cyclohexen-2-ol with phosphorous

pentabromide.

The cyclohexene used in this work was obtained from Matheson Coleman and Bell Chemical Company, the N-bromosuccinimide from Arapahoe Chemical Company, and the amines from Eastman Kodak Company and Sharples Chemical Company. All reagents were used without further purification.

The general method of preparation of the cyclohexenylamines consisted of preparing a large batch of 3-bromocyclohexene by treating a five-fold excess of cyclohexene in carbon tetrachloride at its boiling point with a suitable amount of N-bromosuccinimide. The equipment for this preparation consisted of a three-liter, three-necked flask fitted with an efficient stirrer and a very efficient condenser. The third neck was used for the addition of the N-bromosuccinimide. The reaction after initiation was very rapid and proceeded best at the refluxing temperature of the mixture. The N-bromosuccinimide was added in small increments to aid in controlling the reaction. After the addition had been completed, the succinimide was filtered from the liquid, and the excess cyclohexene and carbon tetrachloride were stripped by distillation. The 3-bromocyclohexene was then distilled under reduced pressure.

The amine used in the reaction was dissolved in ether, and the amount of the 3-bromocyclohexene, calculated to equal half of the molar quantity of the amine, was added. The mixture was allowed to stand overnight at room temperature, and the separated amine salt was filtered. The filtrate was shaken with water, then with sodium hydroxide, and dried with a combination of anhydrous sodium sulfate and potassium hydroxide. This was followed by distillation of the ether and then the amine under reduced pressure.

Preparation of characterization derivatives has been carried out when possible. The preparation of these derivatives has proven very difficult, as about half of these compounds are tertiary amines with rather large substituents, and the other half are secondary amines, also with rather large substituents. In the tertiary amines, only the simpler members would form derivatives as the higher members were sterically hindered. The secondary amines, while reacting readily, formed oils with the lowest as well as the higher members of the series.

The crude amines were distilled twice through a short Vigreaux column. The final sample consisted of a center cut of the second distillation.

All syntheses are described individually in the following pages, and some of the physical properties of the compounds are tabulated. A typical infrared spectrum for this series of compounds is presented, and the important absorption bands of each compound are listed in Table III.

3-Bromocyclohexene

Five hundred grams (6.1 moles) of cyclohexene and one liter of carbon tetrachloride were added to a three-liter, three-necked flask. The flask was equipped with an efficient mechanical stirrer and a 600 mm. Allihn condenser with no constriction at the lower end of the tube to restrict the flow of liquid returning to the reaction. The flask was heated with a three-liter heating mantle adjusted to keep the reaction mixture boiling at minimum reflux. A total of 410 g. (2.3 moles) of N-bromosuccinimide was added over as short a period as possible in 15 g. increments. If amounts larger than this had been added, the reaction would have proceeded with such violence that it would have boiled out of the condenser, causing a low yield. The addition should not take more than one hour. One or two grams of benzoyl peroxide were added to catalyze the reaction. After each addition the mixture boiled violently and filled at least three bulbs of the condenser with condensate. Unless the reaction boiled violently after each addition, the yield was low. After the additions had been completed, the reaction was refluxed for one hour and allowed to cool to room temperature.

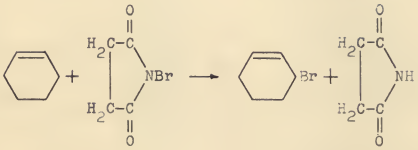
The succinimide was filtered from the liquid, and,

after washing with carbon tetrachloride, was dried and reprocessed into new N-bromosuccinimide. The combined filtrate and washings were placed in a three-liter flask along with 200 ml. of mineral oil as a chaser, several boiling chips, and a stirring bar for a magnetic stirrer. A short Vigreaux column and straight horizontal condenser with a vacuum take-off and fraction cutter were used for the distillation. The cyclohexene and the carbon tetrachloride were stripped off at normal pressure and retained without separation for the next run. The 3-bromocyclohexene was distilled under reduced pressure and boiled at 74°/ 28mm. A yield of 350 g. (94%) was obtained from this run. The normal yield for this reaction was from 85 to 95% with higher yields coming from larger runs. The product as obtained from the first distillation was suitable for use in the preparation of cyclohexen-2-ylamines. Cyclohexene and 3,6-dibromocyclohexene were the only impurities, and they were insignificant.

3-Bromocyclohexene could be stored for only a very short time and then only in an inert atmosphere and in the dark. In this work the 3-bromocyclohexene was used the same day that it was prepared with as little delay as possible. It was necessary to complete reactions in one day in order to avoid low yields of amine.

3-Bromocyclohexene

Equation for Synthesis:



Molecular Formula.....C_6H_9Br

Molecular Weight.....161.046

Boiling Point.....74°/28 mm.

Yield, %.....94.0

This compound is described in the literature.[25-28]

Cyclohexen-2-ylamine

This compound was described in the literature by Hofmann and Damm.[8] Their procedure was not followed, because high enough concentrations of ammonia in benzene were not obtained.

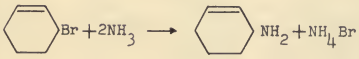
Twenty-five grams of 3-bromocyclohexene (0.158 mole) were mixed with 60 ml. of 28% aqueous ammonia (1 mole) and two drops of Triton X-100 in a 250 ml. Erlenmeyer flask. The flask was placed on a magnetic stirrer and allowed to agitate overnight. The solution, which had turned black, was extracted with ether, separated from the water layer, dried with sodium sulfate and solid potassium hydroxide, and distilled under reduced pressure after the ether was stripped. A yield of 11.3 g. (74%) of a product which boiled at 61°/ 8.2 mm. was obtained.

An attempt was made to distill this sample from sodium to effect a final purification. However, the sodium acted as a polymerization catalyst, and most of the sample polymerized in the still pot.

As this compound was known and was prepared only to obtain its infrared spectrum, the material saved from the above distillation was the only sample made, and no derivatives were prepared.

Cyclohexen-2-ylamine

Equation for Synthesis:



Molecular Formula.....$C_6H_{11}N$

Molecular Weight.....97.156

Boiling Point.....61°/8.2 mm.

Yield, %.....74.0

N-Methylcyclohexen-3-ylamine

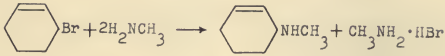
Sixty-eight grams (1 mole) of methylamine hydrochloride were dissolved in water and chilled to 0° with an ice-bath. To the chilled solution were added 40 g. (1 mole) of sodium hydroxide dissolved in 200 ml. of water, and the mixture was chilled to the same temperature. The mixture was cooled during the reaction to prevent loss of the methylamine formed. To the methylamine-salt solution were added 25 g. (0.156 mole) of 3-bromocyclohexene and two drops of Triton X-100. The mixture was placed on the magnetic stirrer and allowed to agitate overnight.

The brown reaction mixture was extracted with ether, separated from the water layer, dried with sodium sulfate and solid potassium hydroxide, the ether stripped, and the product distilled under reduced pressure. The yield was 10 g. (57%) of a product boiling at 67°/14 mm.

N-Methylcyclohexen-2-ylamine

Equation for Synthesis:

$$CH_3NH_3Cl + NaOH \longrightarrow CH_3NH_2 + NaCl + H_2O$$



Molecular Formula.....$C_7H_{13}N$

Molecular Weight.....111.182

Boiling Point.....67°/14 mm.

Yield, %.....57.0

Analysis--Nitrogen, %:

Calculated.....12.6

Found.....12.8

N,N-Dimethylcyclohexen-2-ylamine and Characterization Derivatives

N,N-Dimethylcyclohexen-2-ylamine was prepared by Hofmann and Damm.[8] They treated a solution of dimethylamine with 3-bromocyclohexene in benzene and obtained the expected product.

Considering the success obtained by using aqueous ammonia and methylamine, it was decided to use 25% aqueous dimethylamine in this reaction. It is available commercially from either Distillation Products Industries or Sharples Corporation.

Thirty-two and one-half grams (0.2 mole) of 3-bromocyclohexene and two drops of Triton X-100 were added to 78 g. (0.4 mole) of 25% dimethylamine in water. The mixture was stirred overnight, neutralized with an excess of 50% sodium hydroxide, and extracted with ether. The ethereal extract was dried with anhydrous sodium sulfate and potassium hydroxide pellets and distilled.

The reaction yielded 15.5 g. (60%) of a product boiling at $79^{\circ}/34$ mm., $85^{\circ}/50$ mm., or $91^{\circ}/57$ mm.

Cyclohexen-2-yltrimethylammonium iodide was prepared by adding an excess of methyl iodide to dimethylcyclohexen-2-ylamine. A vigorous reaction took place, and the product was crystallized from absolute alcohol

and anhydrous ether.

The picrate was prepared by mixing an ethanolic solution of the base with a saturated ethanolic solution of picric acid. The solid was crystallized from 95% ethanol.

The cyclohexen-2-yltrimethylammonium iodide melts with loss of solvent at 164-165.5°, resolidifies, and remelts at 260.2-262.2°. The picrate browns at 173.6° and melts at 175-177.6°.

N,N-Dimethylcyclohexen-2-ylamine

Equation for Synthesis:

Molecular Formula	$C_8H_{15}N$
Molecular Weight	125.208
Boiling Point	79°/34 mm.
n^{25}_D	1.4601
Yield, %	60.0

Characterization Derivatives

Cyclohexen-2-yltrimethylammonium iodide:

Molecular Formula.....$C_9H_{16}NI$

Molecular Weight.....269.152

Melting Point.....260.2-262.2°

Analysis--Iodine, %:

Calculated.....47.5

Found.....47.6

N,N-Dimethylcyclohexen-2-ylamine picrate:

Molecular Formula.....$C_{14}H_{18}N_4O_7$

Molecular Weight.....354.316

Melting Point.....Browns, 173.6
Melts, 175-177.6°

Analysis--Nitrogen, %:

Calculated....15.8

Found.....15.4

N-Ethylcyclohexen-2-ylamine

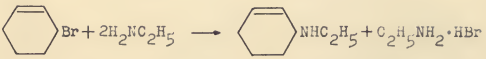
One hundred grams (1.5 moles) of a 70% solution of ethylamine were mixed with 25 g. (0.158 mole) of 3-bromocyclohexene and two drops of Triton X-100. This was stirred overnight at room temperature, neutralized with an excess of 50% sodium hydroxide, and extracted with ether. The extract was dried with anhydrous sodium sulfate and potassium hydroxide pellets. The ether was stripped and the amine distilled under reduced pressure. The yield was 11.2 g. (64%) of a product boiling at $70^{\circ}/15$ mm.

Attempts were made to prepare the hydrobromide, the phenylthiourea, and the benzenesulfonamide as derivatives. The base was dissolved in either absolute alcohol or absolute ether. Dry gaseous hydrogen bromide was bubbled into the solutions, yielding an oil in the ether solution and an oil when the alcohol solution was saturated with ether. Attempts to crystallize these oils were not successful. One milliliter of the base and 1 ml. of phenylisothiocyanate were mixed in a test tube, and after the first vigorous reaction subsided, the mixture was gently heated over an open flame and then allowed to cool. Crystallization from alcohol in a deep freezer at -20° produced a solid which melted at

room temperature and could not be purified. One milliliter of the base, 1 ml. of benzenesulfonyl chloride, and 10 ml. of 20% sodium hydroxide were shaken in a test tube. The starting amine was the only product recovered. The same reaction was run in methylethylpyridine yielding after steam distillation an oil that could not be crystallized.

N-Ethylcyclohexen-2-ylamine

Equation for Synthesis:



Molecular Formula.....$C_8H_{15}N$

Molecular Weight.....125.208

Boiling Point.....70°/15 mm.

n^{20}_D.....1.4702

Yield, %.....64.0

Analyses--Carbon, %:

Calculated.....76.7

Found.....75.8

Hydrogen, %:

Calculated.....12.1

Found.....11.9

N,N-Diethylcyclohexen-2-ylamine and Characterization Derivative

Twenty-five grams (0.3 mole) of diethylamine were mixed with 25 g. (0.15 mole) of 3-bromocyclohexene. The reaction took place at once and required cooling to prevent loss of reactants. The mixture was diluted with ether and filtered. The ether filtrate was shaken with an excess of 50% sodium hydroxide solution, separated, and dried with anhydrous sodium sulfate and potassium hydroxide pellets. The ether was stripped and the amine distilled under reduced pressure. A yield of 17 g. (70%) of a product boiling at 60°/6 mm. was obtained.

The picrate was obtained by mixing a solution of 1 ml. of the base in 10 ml. of 95% ethanol with 10 ml. of a saturated solution of picric acid in ethanol. The yellow precipitate was filtered from the mother liquor and crystallized from 95% ethanol. The product melted at 102-105°.

Attempts were made to prepare the methiodide, the hydrobromide salt, the tartrate salt, the phosphate salt, and the 3,5-dinitrobenzoic acid salt, but no solid product could be isolated from any of these reactions.

Dibromination of the double bond was attempted by the addition of bromine in carbon tetrachloride or in

glacial acetic acid to the base dissolved in the same solvent. No solid product was isolated.

N,N-Diethylcyclohexen-2-ylamine

Equation for Synthesis:

Molecular Formula.....$C_{10}H_{19}N$

Molecular Weight.....153.25

Boiling Point.....60°/6 mm.

$n^{32.5}_{D}$.....1.4635

Yield, %.....70.0

Analysis--Nitrogen, %:

Calculated.....9.14

Found.....9.35

Characterization Derivative

Picrate:

Molecular Formula.....$C_{16}H_{22}N_4O_7$

Molecular Weight.....362.36

Melting Point.....102-105°

Analysis--Nitrogen, %:

Calculated.....14.6

Found.....14.6

N-n-Propylcyclohexen-2-ylamine and Characterization Derivatives

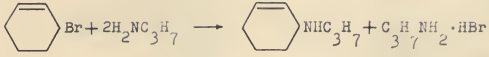
Twenty-five grams (0.15 mole) of 3-bromocyclohexene were added to 100 g. (1.7 moles) of n-propylamine. The mixture was allowed to stand overnight and was then filtered to remove the crystals of n-propylamine hydrobromide. The filtrate was diluted with ether and shaken with an excess of 50% sodium hydroxide, separated, and dried with anhydrous sodium sulfate and potassium hydroxide pellets. The ether was stripped and the product distilled under reduced pressure. This yielded 13 g. (60%) of a product boiling at 66°/6 mm. or 89°/27 mm.

The phenylthiourea was prepared by mixing 1 ml. of the base with 1 ml. of phenylisothiocyanate, heating over an open flame for several minutes after the initial reaction subsided, and then crystallizing from 95% ethanol. The pure product melted at 105.5-106.6°.

The benzenesulfonamide was prepared by adding 1 ml. of the base and 1 ml. of benzenesulfonyl chloride to 10 ml. of methylethylpyridine. After reacting, the mixture was diluted with water and steam distilled. The remaining oil was allowed to solidify and was then crystallized from 95% ethanol. The pure product melts at 89.4-91.4°.

N-n-Propylcyclohexen-2-ylamine

Equation for Synthesis:



Molecular Formula.....$C_9H_{17}N$

Molecular Weight.....139.234

Boiling Point.....89°/27 mm.

n^{20}_D.....1.4690

Yield, %.....60.0

Analyses--Carbon, %:

Calculated.....77.6

Found.....77.8

Hydrogen, %:

Calculated.....12.3

Found.....12.2

Characterization Derivatives

Phenylthiourea:

Molecular Formula.....$C_{16}H_{22}N_2S$

Molecular Weight.....274.418

Melting Point.....105.5-106.5°

Analyses--Carbon, %:

Calculated.....70.0

Found.....69.7

Hydrogen, %:

Calculated.....8.06

Found.....8.07

Benzenesulfonamide:

Molecular Formula.....$C_{15}H_{21}NSO_2$

Molecular Weight.....279.392

Melting Point.....89.4-91.4°

Analyses--Carbon, %:

Calculated.....64.7

Found.....64.3

Hydrogen, %:

Calculated.....7.77

Found.....7.42

N-Isopropylcyclohexen-2-ylamine and Characterization Derivative

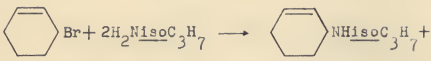
Twenty-five grams (0.15 mole) of 3-bromocyclohexene were added to 30 g. (0.5 mole) of isopropylamine in 100 ml. of ether. The mixture, after standing overnight, was filtered to remove the salt formed, and the filtrate was shaken with an excess of 50% sodium hydroxide. The ether layer was dried, the ether stripped, and the product distilled under reduced pressure. The yield for this reaction was 14.7 g. (66%) of a product boiling at 74°/24 mm.

The phenylthiourea was prepared by mixing 1 ml. of the base and 1 ml. of phenylisothiocyanate in a test tube, and, after the initial reaction subsided, it was heated over an open flame for several minutes. After cooling, the product was crystallized from 95% ethanol. The pure product melted at 116.6-117.6°.

The preparation of the benzenesulfonamide and the benzamide was attempted by several of the conventional methods, but all resulted in the production of oils that refused to solidify even at -20°.

N-Isopropylcyclohexen-2-ylamine

Equation for Synthesis:



Molecular Formula.....$C_9H_{17}N$

Molecular Weight.....139.234

Boiling Point.....74°/24 mm.

n^{25}_D.....1.4624

Yield, %.....68.0

Analysis--Nitrogen, %:

Calculated.....10.1

Found.....10.2

Characterization Derivative

Phenylthiourea:

Molecular Formula.....$C_{16}H_{22}N_2S$

Molecular Weight.....274.418

Melting Point.....116.6-117.6°

Analysis--Nitrogen, %:

Calculated.....10.2

Found.....10.4

N,N-Di-n-propylcyclohexen-2-ylamine and Characterization Derivative

Twenty-five grams (0.15 mole) of 3-bromocyclohexene were mixed with 65 g. (0.64 mole) of di-n-propylamine in 100 ml. of ether. After standing overnight, the reaction mixture was filtered, the filtrate shaken with 50% sodium hydroxide, and separated. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 22 g. (77.5%) of a product boiling at 134°/44 mm. or 118°/27 mm.

The picrate was prepared by mixing 1 ml. of the base in 10 ml. of 95% ethanol with 10 ml. of a saturated ethanolic solution of picric acid. The yellow precipitate was filtered and crystallized from 95% ethanol. The picrate melts at 92.4-93.4°.

The methiodide and the hydrobromide could not be isolated as a solid but always separated as an oil.

N,N-Di-n-propylcyclohexen-2-ylamine

Equation for Synthesis:

Molecular Formula.....$C_{12}H_{23}N$

Molecular Weight.....181.31

Boiling Point.....134°/44 mm.

n^{23}_{D}.....1.4654

Yield, %.....77.8

Analyses--Carbon, %:

Calculated.....79.6

Found.....78.3

Hydrogen, %:

Calculated.....12.8

Found.....12.3

Characterization Derivative

Picrate:

Molecular Formula.....$C_{18}H_{26}N_4O_7$

Molecular Weight.....410.42

Melting Point.....92.4-93.4°

Analyses--Carbon, %:

Calculated.....52.7

Found.....52.5

Hydrogen, %:

Calculated.....6.37

Found.....6.29

N-n-Butylcyclohexen-2-ylamine and Characterization Derivative

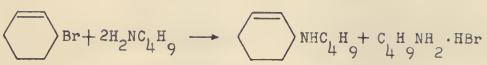
Twenty-five grams (0.15 mole) of 3-bromocyclohexene were mixed with 100 g. (2.1 moles) of n-butylamine in 100 ml. of ether. After standing overnight, the reaction mixture was filtered, the filtrate shaken with an excess of 50% sodium hydroxide, and separated. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 20.5 g. (86%) of a product boiling at 127°/65 mm. or 84°/9.5 mm.

The benzenesulfonamide was prepared by mixing 1 ml. of the base with 1 ml. of benzenesulfonyl chloride in 10 ml. of methylethylpyridine. After reaction, the resulting mixture was steam distilled and the solid residue crystallized from 95% ethanol. The pure product melted at 79.3-81.3°.

The base when mixed with phenylisothiocyanate showed evidence of reacting by immediate evolution of heat, but the product of the reaction could not be crystallized.

N-n-Butylcyclohexen-2-ylamine

Equation for Synthesis:



Molecular Formula.....$C_{10}H_{19}N$

Molecular Weight.....153.26

Boiling Point.....84°/9.5 mm.

n^{20}_D.....1.4675

Yield, %.....86.0

Analyses--Carbon, %:

Calculated.....78.4

Found.....78.1

Hydrogen, %:

Calculated.....12.5

Found.....12.5

Characterization Derivative

Benzenesulfonamide:

Molecular Formula.....$C_{16}H_{23}NSO_2$

Molecular Weight.....293.418

Melting Point.....79.3-81.3°

Analyses--Carbon, %:

Calculated.....65.6

Found.....65.9

Hydrogen, %:

Calculated.....7.90

Found.....7.76

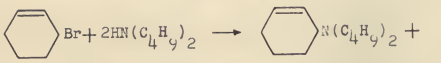
N,N-Di-n-butylcyclohexen-2-ylamine

Twenty-five grams (0.15 mole) of 3-bromocyclohexene were mixed with 80 g. (0.62 mole) of di-n-butylamine in 100 ml. of ether. After standing overnight, the reaction mixture was filtered, the filtrate shaken with an excess of 50% sodium hydroxide, and separated. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 25 g. (77%) of a product boiling at 84°/1.5 mm.

Attempts to prepare the picrate, methiodide, and hydrobromide resulted in oils that could not be crystallized.

N,N-Di-n-butylcyclohexen-2-ylamine

Equation for Synthesis:



Molecular Formula.....$C_{14}H_{27}N$

Molecular Weight.....209.37

Boiling Point.....84°/1.5 mm.

n^{24}_D.....1.4660

Yield, %.....77.0

Analyses--Carbon, %:

Calculated.....80.3

Found.....80.6

Hydrogen, %:

Calculated.....13.0

Found.....12.8

N,N-Diisobutylcyclohexen-2-ylamine and Characterization Derivative

Twenty-five grams (0.15 mole) of 3 bromocyclohexene were mixed with 40 g. (0.31 mole) of diisobutylamine in 100 ml. of ether. After standing overnight, the reaction mixture was filtered, the filtrate shaken with 50% sodium hydroxide, and separated. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 25 g. (77%) of a product boiling at 102°/6 mm.

The picrate was prepared by mixing 1 ml. of the base in 10 ml. of 95% ethanol with 10 ml. of a saturated solution of picric acid in ethanol and boiling five minutes. On cooling and standing at -20° for four weeks, the product solidified and was crystallized from 95% ethanol. The product required several days at -20° to crystallize, even with seeding.

The methiodide and hydrobromide were also attempted in addition to the picrate, but no solid product could be obtained.

N,N-Diisobutylcyclohexen-2-ylamine

Equation for Synthesis:

Molecular Formula.....$C_{14}H_{27}N$

Molecular Weight.....209.37

Boiling Point.....103°/6 mm.

n^{23}_{D}.....1.4627

Yield, %.....77.0

Analysis--Nitrogen, %:

Calculated.....6.67

Found.....6.73

Characterization Derivative

Picrate:

Molecular Formula.....$C_{20}H_{30}N_4O_7$

Molecular Weight.....436.48

Melting Point.....91.9-93.4°

Analyses--Carbon, %:

Calculated...54.6

Found.....54.9

Hydrogen, %:

Calculated...6.90

Found.....6.81

N,N-Diisoamylcyclohexen-2-ylamine

Twenty-five grams (0.15 mole) of 3-bromocyclohexene were mixed with 50 g. (0.31 mole) of diisoamylamine in 100 ml. of ether. After standing overnight, the reaction mixture was filtered, the filtrate shaken with 50% sodium hydroxide, and separated. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 26 g. (71%) of a product boiling at 147.5°/16 mm.

The picrate and the methiodide were attempted as derivatives, but no reaction products were obtained.

N,N-Diisoamylcyclohexen-2-ylamine

Equation for Synthesis:

Molecular Formula.....$C_{16}H_{31}N$

Molecular Weight.....237.4

Boiling Point.....147.5°/16 mm.

n^{20}_{D}.....1.4651

Yield, %.....71.0

Analysis--Nitrogen, %:

Calculated.....5.90

Found.....6.26

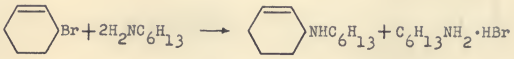
N-n-Hexylcyclohexen-2-ylamine

Twenty-five grams (0.15 mole) of 3-bromocyclohexene were mixed with 120 g. (1.19 moles) of n-hexylamine in 100 ml. of ether. After standing overnight, the reaction mixture was filtered, the filtrate shaken with 50% sodium hydroxide, and separated. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 23 g. (82%) of a product boiling at 112.5°/7 mm., 111.0°/6 mm., or 75°/1 mm.

No solid derivatives could be obtained from the attempts to make the hydrobromide salt, the phenylthiourea, or the benzenesulfonamide.

N-n-Hexylcyclohexen-2-ylamine

Equation for Synthesis:



Molecular Formula.....$C_{12}H_{23}N$

Molecular Weight.....181.312

Boiling Point.....111°/6 mm.

n^{22}_{D}.....1.4670

Yield, %.....82.0

Analyses--Carbon, %:

Calculated.....79.5

Found.....79.4

Hydrogen, %:

Calculated.....12.8

Found.....12.8

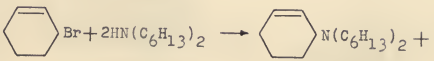
N-N-Di-n-hexylcyclohexen-2-ylamine

Twenty-five grams (0.15 mole) of 3-bromocyclohexene were mixed with 80 g. (0.43 mole) of di-n-hexylamine in 100 ml. of ether. After standing overnight, the reaction mixture was filtered, the filtrate shaken with 50% sodium hydroxide, and separated. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 38 g. (85%) of a product boiling at 127.5°/1 mm.

Attempts to prepare the hydrobromide, the phosphate, the tartrate, and the 3,5-dinitrobenzoate salts were unsuccessful.

N-N-Di-n-hexylcyclohexen-2-ylamine

Equation for Synthesis:



$$\text{Br} + 2\text{HN}(\text{C}_6\text{H}_{13})_2 \longrightarrow \text{N}(\text{C}_6\text{H}_{13})_2 + (\text{C}_6\text{H}_{13})_2\text{NH}\cdot\text{HBr}$$

Molecular Formula.....$C_{18}H_{35}N$

Molecular Weight.....265.468

Boiling Point.....127.5/1 mm.

n^{21}_D.....1.4675

Yield, %.....85.0

Analyses--Carbon, %:

Calculated.....81.4

Found.....81.3

Hydrogen, %:

Calculated.....13.3

Found.....13.3

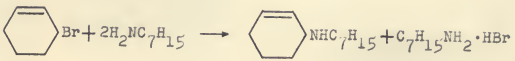
N-n-Heptylcyclohexen-2-ylamine and Characterization Derivative

Twenty-five grams (0.15 mole) of 3-bromocyclohexene were mixed with 110 g. (0.98 mole) of n-heptylamine in 100 ml. of ether. After standing overnight, the reaction mixture was filtered, the filtrate shaken with 50% sodium hydroxide, and separated. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 25.3 g. (83.5%) of a product boiling at $124^{\circ}/6.5$ mm. or at $109^{\circ}/3.0$ mm.

The phenylthiourea was prepared by mixing 1 ml. of the base, and 1 ml. of phenylisothiocyanate in a test tube. After the initial reaction subsided, the mixture was heated gently over an open flame. The cooled product was shaken with 50% ethanol, decanted, dissolved in 95% ethanol, and stored in the deep freeze for several months. At the end of this time the product had solidified and could be crystallized from 95% ethanol. The pure product melted at $95.4\text{-}97.4^{\circ}$.

N-n-Heptylcyclohexen-2-ylamine

Equation for Synthesis:



Molecular Formula.....$C_{13}H_{25}N$

Molecular Weight.....195.34

Boiling Point.....109°/3 mm.

n^{22}_{D}.....1.4667

Yield, %.....83.5

Analyses--Carbon, %:

Calculated.....80.0

Found.....79.8

Hydrogen, %:

Calculated.....12.4

Found.....12.8

Characterization Derivative

Phenylthiourea:

Molecular Formula.....$C_{20}H_{30}N_2S$

Molecular Weight.....330.52

Melting Point.....95.4-97.4°

Analyses--Carbon, %:

Calculated...72.7

Found.....72.6

Hydrogen, %:

Calculated...9.15

Found.....9.07

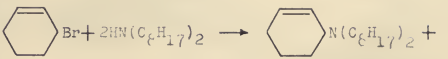
N,N-Di-n-octylcyclohexen-2-ylamine

Twenty-five grams (0.15 mole) of 3-bromocyclohexene were mixed with 100 g. (0.42 mole) of di-n-octylamine in 100 ml. of ether. After standing overnight, the reaction mixture was filtered, the filtrate shaken with 50% sodium hydroxide, and separated. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 31 g. (62.5%) of a product boiling at 164.5°/1 mm.

No derivatives of this amine could be obtained as a solid.

N,N-Di-n-octylcyclohexen-2-ylamine

Equation for Synthesis:



Molecular Formula.....$C_{22}H_{43}N$

Molecular Weight.....321.572

Boiling Point.....164.5°/1 mm.

$n^{22.5}_{D}$.....1.4681

Yield, %.....62.5

Analyses--Carbon, %:

Calculated.....82.3

Found.....82.9

Hydrogen, %:

Calculated.....13.5

Found.....13.6

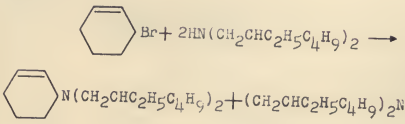
N,N-Di-2-ethylhexylcyclohexen-2-ylamine

Twenty-five grams (0.15 mole) of 3-bromocyclohexene were mixed with 150 g. (0.62 mole) of di-2-ethylhexylamine in 100 ml. of ether. After standing overnight, the reaction mixture was filtered, the filtrate shaken with 50% sodium hydroxide, and separated. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 20 g. (40%) of a product boiling at 135°/0.5 mm.

No derivatives of this amine could be obtained as a solid.

N,N-Di-2-ethylhexylcyclohexen-2-ylamine

Equation for Synthesis:



Molecular Formula.....$C_{22}H_{43}N$

Molecular Weight.....321.572

Boiling Point.....135°/0.5 mm.

n_D^{22}.....1.4703

Yield, %.....40.0

Analyses--Carbon, %:

Calculated.....82.3

Found.....81.5

Hydrogen, %:

Calculated.....13.4

Found.....13.4

N-n-Nonylcyclohexen-2-ylamine

Twenty-five grams (0.15 mole) of 3-bromocyclohexene were mixed with 89 g. (0.62 mole) of n-nonylamine in 100 ml. of ether. After standing overnight, the reaction mixture was filtered, the filtrate shaken with 50% sodium hydroxide, and separated. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 25 g. (72%) of a product boiling at 152°/17.5 mm. or 120°/3.5 mm.

The phenylthiourea was an amorphous, waxy solid which melted near room temperature. All attempts to crystallize this material were unsuccessful, as the product always came down as an amorphous curd containing colored impurities.

N-n-Nonylcyclohexen-2-ylamine

Equation for Synthesis:

Molecular Formula.....$C_{15}H_{29}N$

Molecular Weight.....223.39

Boiling Point.....120°/3.5 mm.

n^{22}_D.....1.4637

Yield, %.....72.0

Analyses--Carbon, %:

Calculated.....80.6

Found.....80.0

Hydrogen, %:

Calculated.....13.1

Found.....13.2

1-(Cyclohexen-2-yl)-piperidine and Characterization Derivatives

Thirty-two and one-half grams (0.20 mole) of 3-bromocyclohexene were mixed with 37 g. (0.43 mole) of piperidine in 100 ml. of ether. The reaction was rapid and required cooling to prevent loss of reactants. After the reaction mixture had cooled, it was allowed to stand overnight and was then filtered and neutralized with 50% sodium hydroxide. The ethereal solution, after separation from the aqueous layer, was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 16.6 g. (50%) of a pure product boiling at 104°/9.5 mm.

This compound, along with its picrate and methiodide derivatives, has been prepared by T. J. King.[11] The reported boiling point was 105°/10 mm.

The picrate was prepared by mixing 1 ml. of the base with 10 ml. of a saturated solution of picric acid in 95% ethanol. The picrate precipitated immediately and was easily crystallized from ethanol. The picrate melted at 110.5-111.5° (reported 108-109°).[11]

The methiodide was prepared by mixing 1 ml. of the base with 1 ml. of methyl iodide. The reaction is immediate and vigorous and the solid methiodide can be

crystallized as soon as the product is cool. The methiodide, crystallized from absolute ethanol and ether, melted at 156.6-157° (reported 160°).[11]

The hydrobromide was made by dissolving 1 ml. of the base in 10 ml. of absolute ether and adding an excess of hydrogen bromide in absolute ethanol. The copious precipitate was crystallized from absolute ethanol and melted at 236.6-238.1°.

1-(Cyclohexen-2-yl)-piperidine

Equation for Synthesis:

Molecular Formula.....$C_{11}H_{19}N$

Molecular Weight.....165.270

Boiling Point.....104°/9.5 mm.

n^{26}_{D}.....1.4985

Yield, %.....50.0

Analysis--Nitrogen, %:

Calculated.....8.38

Found.....8.34

Characterization Derivatives

Picrate:

Molecular Formula.....$C_{17}H_{22}N_4O_7$

Molecular Weight.....394.39

Melting Point.....Found, 110.5-111.5°
Reported, 108-109°

Methiodide:

Molecular Formula.....$C_{12}H_{22}NI$

Molecular Weight.....307.23

Melting Point.....Found, 156.6-157°
Reported, 160°

Hydrobromide:

Molecular Formula.....$C_{11}H_{20}NBr$

Molecular Weight.....246.19

Melting Point.....236.6-238.1°

Analyses--Carbon, %:

Calculated..53.6

Found.....54.1

Hydrogen, %:

Calculated..8.18

Found.....8.17

1-(Cyclohexen-2-yl)-morpholine and Characterization Derivatives

Twenty-five grams (0.15 mole) of 3-bromocyclohexene were mixed with 44 g. (0.50 mole) of morpholine in 100 ml. of ether. The reaction was rapid and required cooling to prevent loss of reactants. After the reaction mixture had cooled, it was allowed to stand overnight. It was then filtered, neutralized with 50% sodium hydroxide, separated from the aqueous layer, and dried. The ether was stripped from the mixture and the product distilled under reduced pressure. The yield was 22.4 g. (87%) of a product boiling at 120°/16 mm.

The picrate was prepared by mixing 1 ml. of the base with 10 ml. of a saturated solution of picric acid in 95% ethanol. The picrate precipitated immediately and was crystallized easily from ethanol. The picrate melted at 149.5-152.5°.

The methiodide was prepared by mixing 1 ml. of the base with 1 ml. of methyl iodide. The reaction was immediate and vigorous and the solid methiodide could be crystallized as soon as the product cooled. The methiodide, crystallized from absolute ethanol and ether, melted at 139-141°.

The hydrobromide was made by dissolving 1 ml. of

the base in 10 ml. of absolute ether and adding an excess of hydrogen bromide in absolute ethanol. The copious precipitate was crystallized from absolute ethanol and melted at 177.4-178.4°.

1-(Cyclohexen-2-yl)-morpholine

Equation for Synthesis:

Molecular Formula.....$C_{10}H_{16}NO$

Molecular Weight.....166.236

Boiling Point.....120°/16 mm.

n^{20}_{D}.....1.5010

Yield, %.....87.0

Analysis--Nitrogen, %:

Calculated.....8.36

Found.....8.56

Characterization Derivatives

Picrate:

Molecular Formula.....$C_{16}H_{19}N_4O_8$

Molecular Weight.....395.346

Melting Point.....149.5-152.5°

Analysis--Nitrogen, %:

Calculated.....14.1

Found.....13.9

Methiodide:

Molecular Formula.....$C_{11}H_{16}NOI$

Molecular Weight.....306.166

Melting Point.....139-141°

Analysis--Nitrogen, %:

Calculated.....4.53

Found.....4.26

Hydrobromide:

Molecular Formula.....$C_{10}H_{18}NOBr$

Molecular Weight.....248.17

Melting Point.....177.4-178.4°

Analyses--Carbon, %:

Calculated.....48.3

Found.....48.5

Hydrogen, %:

Calculated.....7.31

Found.....7.26

CHAPTER IV

REACTIONS OF 2,5-DIMETHYLPIPERAZINE AND DERIVATIVES

Preparation of Derivatives

2,5-Dimethylpiperazine exists in two forms, the trans and the cis. As a point of interest and to aid in the identification of products, the properties of the isomers are presented in Table II.

The 2,5-dimethylpiperazine that was supplied for this work melted at 109.8-114.2°. This was crystallized once from chloroform, which raised the melting point to 115.8-116°. The crystals obtained from this purification were still colored, so the crude material was distilled, yielding a pure white solid boiling at 160-164°/760 mm. It was felt that this material was sufficiently pure for synthetic work.

For comparison with earlier work, the trans isomer was isolated as the dihydrochloride, and the 1,4-dibenzoyl derivative was prepared. The 1,4-dibenzenesulfonamide was made as an additional new derivative and for clinical testing.

The 1-(2-hydroxyethyl) derivative was prepared,

after several attempts, by adding ethylene oxide to a solution of 2,5-dimethylpiperazine in n-hexanol. The use of n-hexenol as a solvent made the purification and separation of unreacted starting material much easier because it prevented the solidification of 2,5-dimethylpiperazine in the condenser during distillation. The 1,4-di-(2-hydroxyethyl) derivative was obtained as a by-product of the above reaction. It was also made intentionally by addition of an excess of ethylene oxide both to 2,5-dimethylpiperazine in methanol and to the 1-(2-hydroxyethyl) derivative in methanol.

1-(2-Hydroxyethyl)-piperazine was prepared by the method of Kitchen and Pollard[42] and was used as an intermediate in the preparation of the cyclohexenyl derivative.

1-(2-Hydroxyethyl)-4-cyclohexen-2-ylpiperazine and 1-(2-hydroxyethyl)-4-cyclohexen-2-yl-2,5-dimethylpiperazine were prepared by adding 3-bromocyclohexene to the amino alcohol.

The phenyl derivative was attempted in several ways and finally was made by the addition of iodobenzene to the amino alcohol.

trans-2,5-Dimethylpiperazine and

Characterization Derivatives

Fifty-seven grams (0.50 mole) of 2,5-dimethylpiperazine were dissolved in 200 ml. of absolute ethanol. This solution was added to a 500 ml. three-necked flask containing 100 ml. of absolute ethanol saturated with dry hydrogen chloride. Hydrogen chloride was bubbled into the flask throughout the addition. The heat of reaction was dissipated by allowing the ethanol to reflux. The solid was filtered through a sintered glass filter disk and extracted five times with boiling absolute ethanol. The product was removed from the tube and dried overnight in a desiccator containing calcium chloride.

The yield was 77 g. (82%) of the dihydrochloride of trans-2,5-dimethylpiperazine.

The benzenesulfonamide was prepared by mixing 6 g. of 2,5-dimethylpiperazine with 17 g. of benzenesulfonyl chloride and an excess of 20% sodium hydroxide. The product was filtered from the mixture and crystallized from formamide. The yield was 10 g. (46%) of pure product melting at 222-223°.

1,4-Dibenzoyl-2,5-trans-dimethylpiperazine was prepared from 5 g. of trans-2,5-dimethylpiperazine dihydrochloride dissolved in 40 ml. of water. To this

solution were added 7 ml. of benzoyl chloride and 60 ml. of 20% sodium hydroxide. The mixture was shaken vigorously, and the white, curdy precipitate was filtered from the solution.

Pope and Kipping, who prepared this derivative, state that 1,4-dibenzoyl-trans-2,5-dimethylpiperazine is insoluble in all usual solvents, and to effect its purification, they resorted to extraction of the solid product with various solvents.[17] They obtained a product melting at 226-229°. Because of the remarkable solvent properties of formamide, it was used for crystallizing the dibenzoyl derivative. 1,4-Dibenzoyl-2,5-trans-dimethylpiperazine crystallized very readily from formamide and yielded 4.7 g. (53%) of a product which melted at 230-231°. The same reaction was run with distilled 2,5-dimethylpiperazine, yielding a product melting at 229-230°. A mixed melting point of this product with the trans isomer derivative also melted at 229-230°. From these results it was decided that the distilled 2,5-dimethylpiperazine, rather than the pure trans isomer obtained from the extraction of the hydrochlorides, would provide suitable starting material for the preparations that follow.

TABLE II

THE PROPERTIES OF trans- AND cis - 2,5-DIMETHYL-
PIPERAZINE AND CERTAIN OF THEIR DERIVATIVES

Property or Derivative	cis-2,5-Dimethyl-	trans-2,5-Dimethyl-
Molecular Formula	$C_6H_{14}N_2$	$C_6H_{14}N_2$
Molecular Weight	114	114
Form	Liquid	Solid
Boiling Point	164.5°	161.9°
Melting Point	17-18°	117-118°
Dibenzoyl	147-148°	228-229°
Di-p-toluenesulfonyl	146-147°	225°
Dibenzyl	105-106°	---
Di-a-naphthalenesulfonyl	-------	269-270°

trans-2,5-Dimethylpiperazine and Characterization Derivatives

Preparation:

The trans isomer was prepared by extracting the mixed trans and cis isomer hydrochlorides with boiling ethanol. The trans isomer was insoluble.

Molecular Formula.....$C_6H_{14}N_2$

Molecular Weight.....114.188

Melting Point.....118°

Boiling Point.....162°/760 mm.

Characterization Derivatives

1,4-Dibenzenesulfonamide:

Molecular Formula.....$C_{18}H_{22}N_2S_2O_4$

Molecular Weight.....394.492

Melting Point.....222-223°

Analysis--Nitrogen, %:

Calculated...7.10

Found.....6.93

1,4-Dibenzoyl:

Molecular Formula.....$C_{20}H_{22}N_2O_4$

Molecular Weight.....354.392

Melting Point.....Found, 230-231°
Reported, 228-229°

1-(2-Hydroxyethyl)-2,5-dimethylpiperazine and Characterization Derivative

Ninety grams (2.04 moles) of ethylene oxide were added to 5 ml. of water and 1140 g. (10 moles) of 2,5-dimethylpiperazine dissolved in 1000 ml. of n-hexanol. The reaction mixture was maintained at 90° with a heating mantle throughout the period of four hours required to complete the addition of the ethylene oxide. The reaction vessel was a three-necked, three-liter flask equipped with a condenser, and efficient stirrer, and an addition tube extending below the surface of the liquid in the flask.

After the addition was complete, the condenser was placed in a horizontal position by means of a 90° bend, and the stirrer and addition tube were removed and replaced with stoppers. The hexanol, water, and 2,5-dimethylpiperazine were stripped and the product distilled under reduced pressure. The yield was 220 g. (69.7%) of a product boiling at 121°/10 mm.

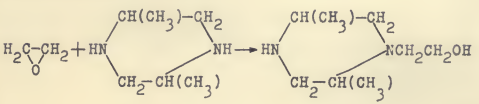
Kitchen and Pollard prepared 1-(2-hydroxyethyl)-piperazine by reacting ethylene oxide with piperazine in methanol.[42] This procedure was followed with 2,5-dimethylpiperazine, but the excess 2,5-dimethylpiperazine was very difficult to separate from the product

because it would solidify in the condenser, plugging it. This reaction was modified by using a solvent which boiled near the boiling point of 2,5-dimethylpiperazine. n-Hexanol, with a boiling point of 156°, was chosen. The mixture of n-hexanol and 2,5-dimethylpiperazine distilled smoothly, with no plugging of the condenser. Nearly all of the 1-(2-hydroxyethyl)-2,5-dimethylpiperazine used in this project was prepared in this manner.

1,4-Di-(2-hydroxyethyl)-2,5-dimethylpiperazine was prepared as a characterization derivative by adding an excess of ethylene oxide to 10 g. of 1-(2-hydroxyethyl)-2,5-dimethylpiperazine in methanol. It was also recovered as a by-product from the preparation of 1-(2-hydroxyethyl)-2,5-dimethylpiperazine. The yield as a by-product was as much as 10% of the molar quantity of ethylene oxide used. The melting point of 1,4-di-(2-hydroxyethyl)-2,5-dimethylpiperazine was 108.5-110°, and the product was crystallized from benzene.

1-(2-Hydroxyethyl)-2,5-dimethylpiperazine

Equation for Synthesis:



Molecular Formula.....$C_8H_{18}N_2O$

Molecular Weight.....158.24

Boiling Point.....121°/10 mm.

n_D^{26}.....1.4925

d^{25}.....1.0053

Molar Refraction:

Calculated.....46.03

Found.....45.88

Yield, %.....69.7

Analysis--Nitrogen, %:

Calculated.....17.7

Found.....17.7

Characterization Derivative

1,4-Di-(2-hydroxyethyl)-2,5-dimethylpiperazine:

Molecular Formula.....$C_{10}H_{22}N_2O_2$

Molecular Weight.....202.30

Melting Point.....108.5-110°

Analysis--Nitrogen, %:

Calculated....13.9

Found.....13.9

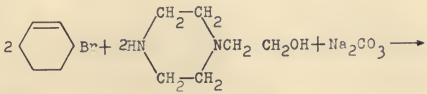
1-Cyclohexen-2-yl-4-(2-hydroxyethyl)-piperazine and Characterization Derivative

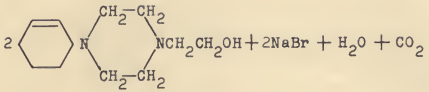
Thirty-two grams (0.2 mole) of 3-bromocyclohexene were added to 26 g. (0.2 mole) of 1-(2-hydroxyethyl)-piperazine and 10.6 g. (0.1 mole) of sodium carbonate in 100 ml. of carbon tetrachloride. The mixture was refluxed overnight. The basic material was neutralized with dilute hydrochloric acid and separated from the non-aqueous layer. The aqueous layer was made strongly basic with sodium hydroxide, saturated with sodium sulfate, and extracted with ether. The ethereal extract was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 15 g. (38.6%) of a product boiling at 161.5°/4.2 mm.

The picrate was prepared by mixing 1 ml. of the base with 10 ml. of a saturated solution of picric acid in ethanol. The picrate was filtered from the reaction mixture and crystallized from 95% ethanol. The picrate melted at 199-201°.

1-Cyclohexen-2-yl-4-(2-hydroxyethyl)-piperazine

Equation for Synthesis:





Molecular Formula.....$C_{12}H_{22}N_2O$

Molecular Weight.....210.312

Boiling Point.....161.5°/4.2 mm.

$n_D^{26.5}$.....1.5215

Yield, %.....36.6

Analysis--Nitrogen, %:

Calculated.....13.3

Found.....13.1

Characterization Derivative

Picrate:

Molecular Formula.....$C_{18}H_{25}N_5O_8$

Molecular Weight.....439.422

Melting Point.....199-201°

Analysis--Nitrogen, %:

Calculated....15.9

Found.....16.6

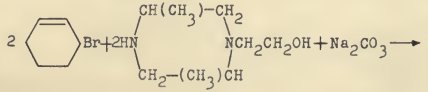
1-Cyclohexen-2-yl-4-(2-hydroxyethyl)-2,5-dimethylpiperazine and Characterization Derivative

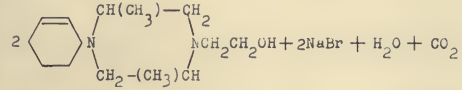
Thirty-two grams (0.2 mole) of 3-bromocyclohexene were mixed with 31 g. (0.2 mole) of 1-(2-hydroxyethyl)-2,5-dimethylpiperazine and 10.6 g. (0.1 mole) of sodium carbonate in 100 ml. of carbon tetrachloride. The reaction mixture was heated overnight. The reaction mixture was made acid with dilute hydrochloric acid and the aqueous layer separated. This solution was made strongly basic with sodium hydroxide and saturated with sodium sulfate, which allowed the base to be extracted easily with ether. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure. The yield was 15.7 g. (33%) of a product boiling at 121°/0.45 mm. or 173°/6.5 mm.

The hydrobromide was prepared by dissolving 1 ml. of the base in 10 ml. of absolute ethanol and mixing it with 10 ml. of a solution of dry hydrogen bromide in ether. The dihydrobromide formed was only slightly soluble in absolute ethanol, so it was crystallized from wet ethanol and precipitated by ether. The final product was dried at 100° for two days in a vacuum oven. The dihydrobromide melted at 193-194°.

1-Cyclohexen-2-yl-4-(2-hydroxyethyl)-2,5-dimethylpiperazine

Equation for Synthesis:





Molecular Formula.....$C_{14}H_{26}N_2O$

Molecular Weight.....238.364

Boiling Point.....173°/6.5 mm.

n_D^{27}.....1.5157

Yield, %.....33.0

Neutral Equivalent:

Calculated.....238

Found.....240

Analysis--Nitrogen, %:

Calculated.....11.8

Found.....11.9

Characterization Derivative

Dihydrobromide:

Molecular Formula.....$C_{14}H_{26}N_2O2HBr$

Molecular Weight.....400.212

Melting Point.....193-194°

Analysis--Bromine, %:

Calculated....39.9

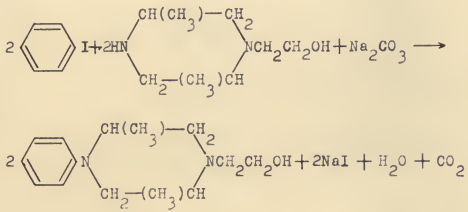
Found.....39.6

1-Phenyl-4-(2-hydroxyethyl)-2,5-dimethylpiperazine Dihydrochloride

Thirty grams (0.147 mole) of iodobenzene, 27 g. (0.17 mole) of 1-(2-hydroxyethyl)-2,5-dimethylpiperazine, and 21 g. (0.20 mole) of anhydrous potassium carbonate were mixed together and refluxed for twenty-four hours. The reaction mixture was made basic with sodium hydroxide, and the released base was extracted with ether. The ethereal solution was dried, the ether stripped, and the product distilled under reduced pressure, boiling at 145-165°/3 mm. This product was treated with a small excess of ethylene oxide to remove any unreacted 1-(2-hydroxyethyl)-2,5-dimethylpiperazine and converted into the dihydrochloride with anhydrous hydrogen chloride. The dihydrochloride was crystallized from ethanol and anhydrous ether. Some of the product formed was used for other experiments. This reaction yielded 2.5 g. (4.08% over-all) of the dihydrochloride, which melted at 235.5-237.5°.

1-Phenyl-4-(2-hydroxyethyl)-2,5-dimethylpiperazine Dihydrochloride

Equation for Synthesis:



Molecular Formula.....$C_{14}H_{22}N_2O2HCl$

Molecular Weight.....307.262

Melting Point.....231-233°

Yield, %.....4.08

Analyses--Nitrogen, %:

Calculated.....9.15

Found.....8.84

Chlorine, %:

Calculated.....23.2

Found.....23.2

Carbon, %:

Calculated.....54.8

Found.....54.6

Hydrogen, %:

Calculated.....7.88

Found.....7.85

Experimental Work and Discussion of Some of the Other Possible Routes Used Unsuccessfully in Attempts to Prepare 1-Phenyl-4-(2-hydroxyethyl)-2,5-dimethylpiperazine

The first experiment conducted was the preparation of 1-cyclohexyl-4-(2-hydroxyethyl)-2,5-dimethylpiperazine. The intention was to dehydrogenate this material to the phenyl derivative.

Ten grams of the cyclohexyl compound were mixed with a large excess of sulfur and heated for several hours. The product was a thick tar from which no individual compounds could be isolated. Ten grams of the cyclohexyl compound were mixed with a slight excess of sulfur and heated for several hours, again yielding a thick tar. The preparation of the cyclohexyl derivative was repeated, and 10 g. of this material were mixed with 2 g. of 5% platinum on asbestos and heated for several hours. This yielded a thick tar from which a small amount of starting material could be recovered. The same procedure, with the same results, was carried out using palladium on asbestos.

Study of the standard organic textbooks indicated that cyclohexene may be dehydrogenated much more easily than cyclohexane. This mode of attack was pursued by first preparing 1-cyclohexen-2-yl-4-(2-hydroxyethyl)-

2,5-dimethylpiperazine to be used as a starting material for several further reactions. The cyclohexenyl derivative was first mixed with an excess of sulfur and heated. This reaction yielded a thick tar, with an extremely bad and penetrating odor, from which no individual compounds could be isolated. The experiment was repeated with a slight excess of sulfur and yielded the same results. The same experiment was repeated using selenium instead of sulfur with the same results except the odor was much worse.

Ten grams of the cyclohexenyl derivative were treated with 2 g. of platinum on asbestos. A large amount of polymer resulted as the only product. The same results were obtained using palladium on asbestos.

Ten grams of the cyclohexenyl derivative were mixed with 30 ml. of cyclohexene and 50 ml. of xylene and refluxed for twenty-four hours. The product from this reaction was liquid but could be crystallized from ethyl acetate. The starting material would not crystallize from the same solvent. Analysis of this product for nitrogen, carbon, and hydrogen checked exactly for 1-cyclohexen-2-yl-4-(2-hydroxyethyl)-2,5-dimethylpiperazine monohydrate. This indicated that this reaction yielded no material other than starting material. It was felt that the product that crystallized as the mono-

hydrate was an isomer of the original starting material. If a quantity of the cyclohexenyl derivative were allowed to stand at 0° for four to six months, about one-third of the material present would have solidified and could have been crystallized in the same manner as described above. The product had the same melting point, and a mixed melting point with the above material was depressed only slightly.

1-Cyclohexen-2-yl-4-(2-hydroxyethyl)-2,5-dimethylpiperazine can be considered as a derivative of cyclohexen-2-ylamine. With this in mind, cyclohexen-2-ylamine, N-methylcyclohexen-2-ylamine, N,N-dimethylcyclohexen-2-ylamine, N,N-diethylcyclohexen-2-ylamine, N-cyclohexen-2-ylpiperidine, N-cyclohexen-2-ylmorpholine, and N-cyclohexen-2-ylaniline were synthesized. It was believed that the cyclohexene ring would, on standing, disproportionate into two moles of the cyclohexyl and one mole of the phenyl derivative of the amine involved. This aging was followed by use of the infrared spectrometer, spectra being taken at various intervals in an effort to detect any change. The N,N-diethylcyclohexen-2-ylamine was considered of much interest, as the two C_2 chains attached to the nitrogen atom approximated the piperazine structure. Pure samples of N,N-diethylcyclohexane and N,N-diethyl-

aniline were obtained from Distillation Products Industries and were distilled through a Todd Precise Distillation Column using a 120 cm. column, 12 mm. in diameter, packed with glass helices. Infrared spectra of these materials were made, along with a mixture of one-third N,N-diethylaniline and two-thirds N,N-diethylcyclohexylamine, and 10% of this mixture in 90% of N,N-diethylcyclohexen-2-ylamine. These spectra are presented in the section discussing the infrared spectra made in the course of this work.

These spectra prove that there is no spontaneous disproportionation of the compounds under study over the period involved. There was a decrease in the unsaturation of the diethyl derivative, but as there was no indication of formation of a phenyl group, this decrease in unsaturation was attributed to the formation of a polymer which precipitated as amorphous globules in the liquid.

Further attempts were made to prepare the phenyl derivative, including addition of o-chlorobenzoic acid and p-chlorobenzoic acid to 1-(2-hydroxyethyl)-2,5-dimethylpiperazine using a copper catalyst, addition of p-nitrobromobenzene to 1-(2-hydroxyethyl)-2,5-dimethylpiperazine. The preparation of 1-phenyl-2,5-dimethylpiperazine was considered via N-1-methyl-2-chloroethyl-N-2-methyl-2-chloroethylaniline, but this intermediate could not be prepared.

CHAPTER V

DISCUSSION AND CONCLUSIONS

Infrared Spectra

Aromatic groups, alkenes, and alkanes are easily differentiated by their characteristic infrared absorption bands. The possibility of cyclohexenyl groups disproportionating to a phenyl group and two cyclohexyl groups could be investigated experimentally using the infrared spectrograph to determine any change.

N,N-Diethylcyclohexen-2-ylamine was chosen as the compound to be studied by this method, as pure N,N-diethylcyclohexylamine and N,N-diethylaniline are available commercially, and its structure approaches the basic structure of the piperazine derivative to be prepared by this method. Other related derivatives of cyclohexen-2-ylamine were prepared and their infrared spectra made to aid in determining typical absorption bands for these compounds.

Table III compares freshly made N,N-diethylcyclohexen-2-ylamine, N,N-diethylcyclohexylamine, and N,N-diethylaniline with N,N-diethylcyclohexen-2-ylamine stored six months at 20°. For reference, ten other

related compounds are included. The spectra of cyclohexane, cyclohexene, benzene, aniline, and N,N-dimethylaniline were adapted from "Infrared Spectroscopy" by Barnes et al.[43]

There are seventeen major points of difference between the spectra of N,N-diethylcyclohexylamine, N,N-diethylcyclohexen-2-ylamine, and N,N-diethylaniline. These differences show conclusively that no disproportionation occurs and that after six months standing, the starting material, N,N-diethylcyclohexen-2-ylamine, is the only compound present. Figures 1-6 are photo reproductions of the pertinent spectra. Figure 1 is freshly prepared N,N-diethylcyclohexen-2-ylamine. Figure 2 is the same material aged for six months at 20°. Figure 3 is N,N-diethylcyclohexylamine. Figure 4 is N,N-diethylaniline. Figure 5 is a mixture of 33 1/3 mole per cent of N,N-diethylaniline and 66 2/3 mole per cent of N,N-diethylcyclohexylamine. Figure 6 is a mixture of 10% of the mixture used in Figure 5 mixed with 90% fresh N,N-diethylcyclohexen-2-ylamine. It may be seen that the spectrum in Figure 2 is quite different from the one on Figure 6 and that Figures 1 and 2 are identical.

The absorption bands of the other compounds used in this study are presented in Table III, along with

N-methylaniline, N,N-diethylcyclohexylamine, and N,N-diethylaniline as reference materials. Several interesting points may be observed from these data. The band appearing near 690 cm^{-1} for phenyl appears at 674-669 cm^{-1} for cyclohexenyl. The band near 1600 cm^{-1} for phenyl appears at 1658-1650 cm^{-1} for cyclohexenyl. Phenylcyclohexen-2-ylamine exhibits bands at 748 and 725 cm^{-1}. N-Methyl and N,N-diethylaniline have the band at around 748 cm^{-1}, and the cyclohexen-2-ylamines have the band at 725-722 cm^{-1}. This indicates that the 725-722 cm^{-1} band is characteristic for the cyclohexen-2-ylamine series. The band found between 1477 and 1439 cm^{-1} shows a tendency to split into two bands when the compound is either a primary or secondary amine. Three tertiary amines show this split while two of the secondary amines do not.

TABLE III

INFRARED ABSORPTION BANDS OF SOME RELATED DERIVATIVES OF CYCLOHEXYLAMINE, CYCLOHEXENYLAMINE, AND ANILINE

Molecule	Absorption Frequencies CM^{-1} 4000	3500	3000
1. Cyclohexane			
2. Cyclohexene			
3. Benzene			
4. Cyclohexylamine			
5. Cyclohexenylamine			
6. Aniline			
7. N-Methylcyclohexenylamine			
8. N-Methylaniline			
9. N,N-Dimethylcyclohexenylamine			
10. N,N-Dimethylaniline			
11. N,N-Diethylcyclohexylamine			
12. N,N-Diethylcyclohexenylamine			
13. N,N-Diethylcyclohexenylamine (6 months)			
14. N,N-Diethylaniline			
15. Reference Bands			

TABLE III--Continued

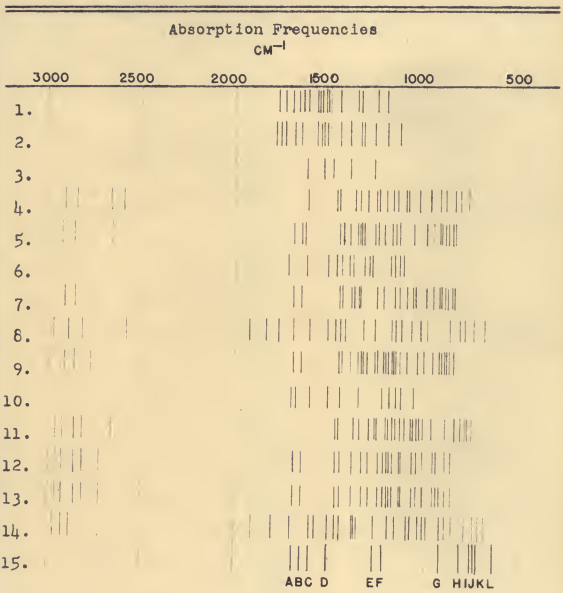


TABLE IV

INFRARED ABSORPTION BANDS OF COMPOUNDS OF THE TYPE

Where R contains a nitrogen atom attached directly to the cyclohexenyl group

R	Absorption Frequencies cm^{-1} 4000	3500	3000	2500
1. Amino				
2. Methylamino				
3. Dimethylamino				
4. Ethylamino				
5. Diethylamino				
6. n-Propylamino				
7. iso-Propylamino				
8. Di-n-propylamino				
9. n-Butylamino				
10. Di-n-butylamino				
11. Di-iso-butylamino				
12. Di-iso-amylamino				

TABLE IV--Continued

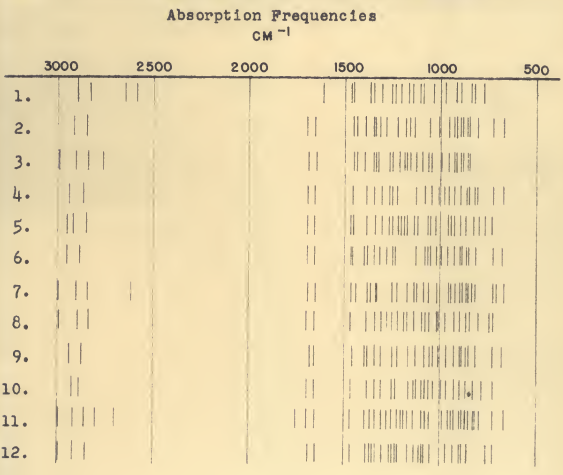


TABLE IV--Continued

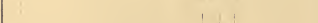
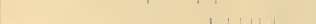
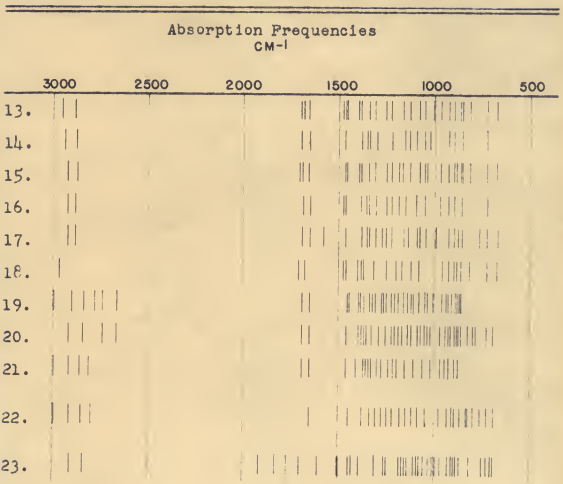
R	Absorption Frequencies CM^{-1} 4000 3500 3000 2500
13. n-Hexylamino	
14. Di-n-hexylamino	
15. n-Heptylamino	
16. Di-n-octylamino	
17. Di-2-ethylhexylamino	
18. n-Nonylamino	
19. Piperidine	
20. Morpholine	
21. 4-(2-Hydroxyethyl)-piperazine	
22. 4-(2-Hydroxyethyl)-2,5-dimethylpiperazine	
23. Phenyl	

TABLE IV--Continued



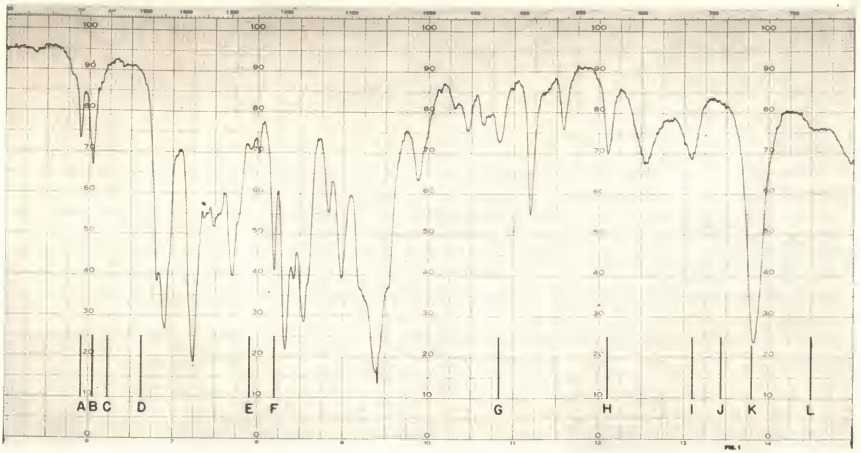


Fig. 1.-Infrared spectrum on freshly prepared N,N-diethylcyclohexen-2-ylamine.

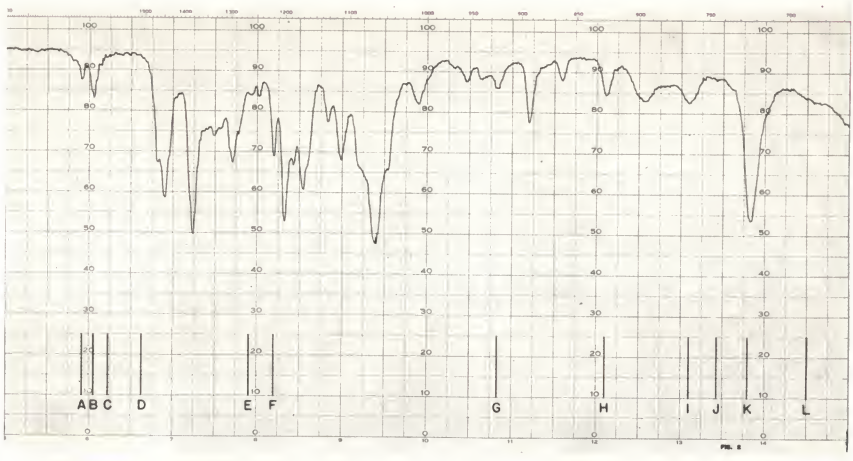


Fig. 2.-Infrared spectrum of N,N-diethylcyclohexenylamine after aging six months.

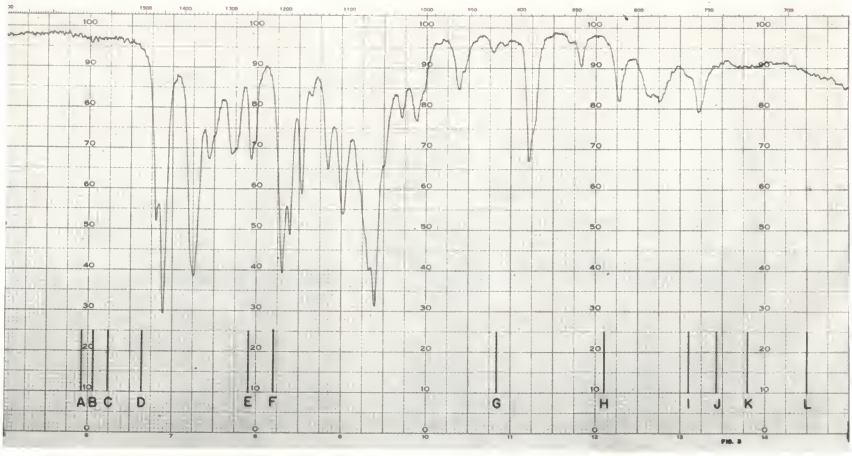


Fig. 3.-Infrared spectrum of N,N-diethylcyclohexylamine.

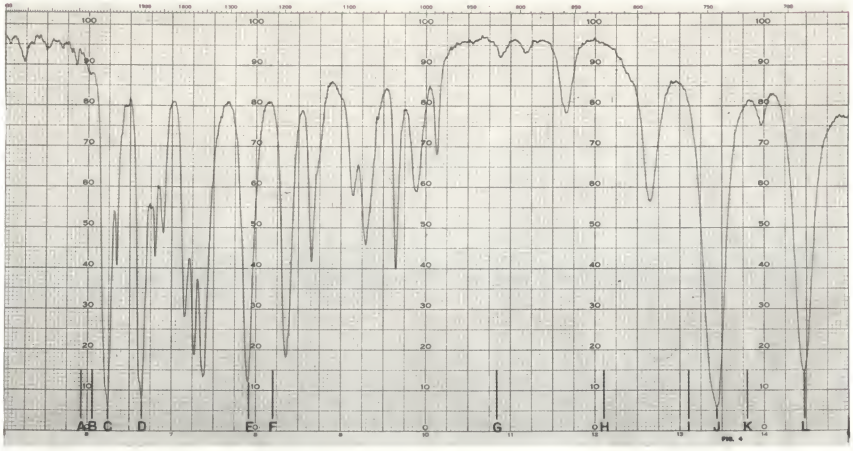


Fig. 4.-Infrared spectrum of N,N-diethylaniline.

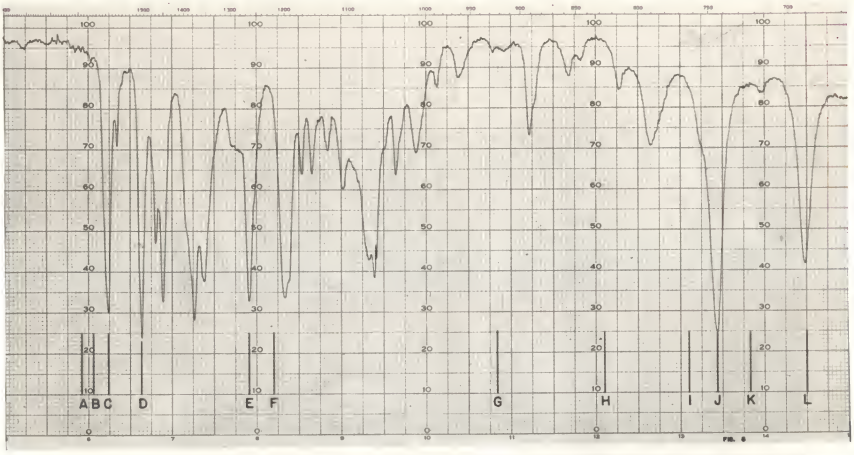


Fig. 5.-Infrared spectrum of a mixture of 33 1/3 mole per cent N,N-diethylaniline and 66 2/3 mole per cent N,N-diethylcyclohexylamine.

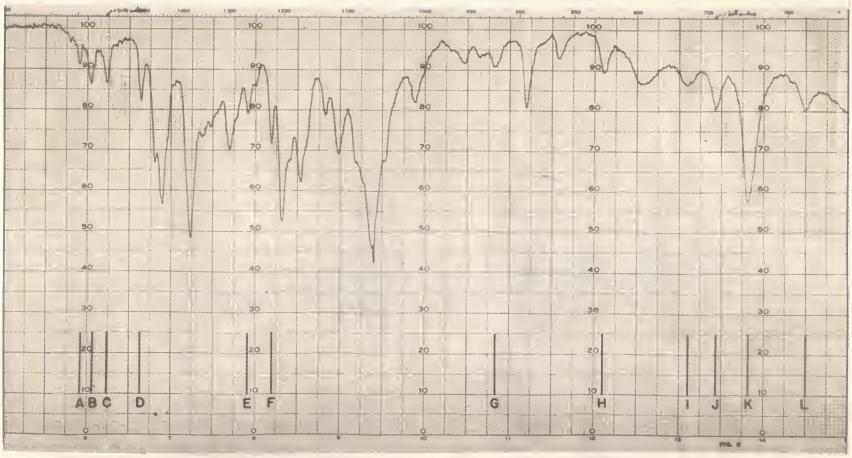


Fig. 6.-Infrared spectrum of 3 1/3 per cent N,N-diethylaniline, 6 2/3 per cent N,N-diethylcyclohexylamine, and 90 per cent N,N-diethylcyclohexen-2-ylamine.

Discussion and Conclusions

A number of substituted cyclohexen-2-ylamines have been prepared by use of 3-bromocyclohexene as an alkylating agent. The alkylation proceeded smoothly and rapidly produced the desired cyclohexen-2-ylamine in good yields. These amines may be purified by distillation since the starting amine was the only major impurity.

The 3-bromocyclohexene may be made in high yields by bromination of cyclohexene with N-bromosuccinimide. This was a standard reaction with both starting materials available commercially.

Attempts to convert the cyclohexenyl group into a phenyl group were not successful. As this conversion was tried only on the 2,5-dimethylpiperazine derivative, eventual success in arylating amines by this method is not precluded.

Derivatives to aid in the characterization of the amines prepared were difficult or impossible to make. It is felt that many of the desired derivatives could be made if completely anhydrous conditions could be maintained. Due to the high humidity in the laboratory, the transfer of solvents, starting materials, and products could not be made without their absorbing moisture. The quaternary salts and acid salts of the cyclohexen-2-ylamines

with alkyl groups on the nitrogen were particularly hygroscopic. Heterocyclic compounds, with the cyclohexen-2-yl radical attached to the nitrogen, formed derivatives with ease and were not noticeably hygroscopic.

Table VII compared the boiling points of various alkylated amino derivatives of cyclohexane, cyclohexene, and benzene. While the boiling points were not at the same pressure, the fact was obvious that the boiling points of the cyclohexyl amines and the cyclohexenylamines were fairly close to each other, with the cyclohexenylamines boiling higher than the cyclohexylamines. The anilines all boiled much higher than the comparable compounds with the more saturated rings. Too little data were available to draw any comparison between the refractive indices or the melting points of similar derivatives of these three series.

CHAPTER VI

S U M M A R Y

As a result of this investigation, eighteen cyclohexen-2-ylamines have been synthesized. These compounds, with the exceptions of cyclohexen-2-ylamine, N,N-dimethylcyclohexen-2-ylamine, and N,N-diethylcyclohexen-2-ylamine, are new to the literature. Data on these compounds are presented in Table V. Characterization derivatives for these compounds are reported on the individual data sheets for the compounds.

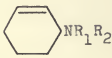
Four N-substituted heterocyclic compounds have been synthesized. With the exception of N-cyclohexen-2-ylpiperidine, these compounds are new to the literature. Data on these compounds are presented in Table VI. Characterization derivatives for these compounds are reported on the individual data sheets for the compound.

1-(2-Hydroxyethyl)-2,5-dimethylpiperazine, which is new to the literature, has been synthesized. Data on this compound are presented in Table VI.

Infrared spectra of certain of these compounds are presented in Figures 1-6, and their characteristic absorption bands are presented in Tables III and IV.

TABLE V

DATA CONCERNING ALKYLATED CYCLOHEXEN-2-YLAMINES



Where R_1 is H or alkyl; R_2 is H or alkyl

R_1	R_2	Yield, %	B.p.		n_D	m.p. °C
			°C	mm.		
H	H	74.0	61.0	8.2	....	...
H	CH_3	57.0	67.0	14.0	....	...
CH_3	CH_3	60.0	79.0	34.0	1.4801	25.0
H	C_2H_5	64.0	70.0	15.0	1.4702	20.0
C_2H_5	C_2H_5	70.0	60.0	6.0	1.4635	32.5
H	n-C_3H_7	60.0	89.0	27.0	1.4690	20.0
H	iso-C_3H_7	68.0	74.0	24.0	1.4624	25.0
n-C_3H_7	n-C_3H_7	77.8	134.0	44.0	1.4654	23.0
H	n-C_4H_9	86.0	84.0	9.5	1.4675	20.0
n-C_4H_9	n-C_4H_9	77.0	84.0	1.5	1.4660	24.0
iso-C_4H_9	iso-C_4H_9	77.0	103.0	6.0	1.4627	23.0
iso-C_5H_{11}	iso-C_5H_{11}	71.0	147.5	16.0	1.4651	20.0
H	n-C_6H_{13}	82.0	111.0	6.0	1.4670	22.0
n-C_6H_{13}	n-C_6H_{13}	85.0	127.5	1.0	1.4675	21.0
H	n-C_7H_{15}	83.5	109.0	3.0	1.4667	22.0
n-C_8H_{17}	n-C_8H_{17}	62.5	164.5	1.0	1.4681	22.5
2-(C_2H_5)C_6H_{12}	2-(C_2H_5)C_6H_{12}	40.0	135.0	0.5	1.4703	22.0
H	n-C_9H_{19}	72.0	120.0	3.5	1.4637	22.0

TABLE V--Continued

Molecular Formula	Molecular Weight	N, %		C, %		H, %	
		Calc.	Found	Calc.	Found	Calc.	Found
$C_6H_{11}N$	97.15	....	....	.....	....	....	....
$C_7H_{13}N$	111.18	12.6	12.8	.....	....	....	....
$C_8H_{15}N$	125.21	.....	....	.....	....	....	....
$C_8H_{15}N$	125.21	.....	.....	76.7	75.8	12.1	11.9
$C_{10}H_{19}N$	153.25	9.14	9.35	....	....	....	....
$C_9H_{17}N$	139.23	.....	.....	77.6	77.8	12.3	12.2
$C_9H_{17}N$	139.23	10.1	10.2	....	....	....	....
$C_{12}H_{23}N$	181.31	.....	.....	79.6	78.3	12.8	12.3
$C_{10}H_{19}N$	153.26	.....	.....	78.4	78.1	12.5	12.5
$C_{14}H_{27}N$	209.37	.....	.....	80.3	80.6	13.0	12.8
$C_{14}H_{27}N$	209.37	6.67	6.73	....	....	....	....
$C_{16}H_{31}N$	237.40	5.90	6.26	....	....	....	....
$C_{12}H_{23}N$	181.31	.....	.....	79.5	79.4	12.8	12.8
$C_{18}H_{35}N$	265.47	.....	.....	81.4	81.3	13.3	13.3
$C_{13}H_{25}N$	195.34	.....	.....	80.0	79.8	12.4	12.8
$C_{22}H_{43}N$	321.57	.....	.....	82.3	82.9	13.5	13.6
$C_{22}H_{43}N$	321.57	.....	.....	82.3	81.5	13.4	13.4
$C_{15}H_{29}N$	223.39	.....	.....	80.6	80.0	13.1	13.2

TABLE VI

DATA CONCERNING N-CYCLOHEXEN-2-YL SUBSTITUTED HETEROCYCLIC COMPOUNDS

Where R is heterocyclic

Compound	Yield, %
1-(Cyclohexen-2-yl)-piperidine	50.0
1-(Cyclohexen-2-yl)-morpholine	87.0
1-Cyclohexen-2-yl-4(2-hydroxyethyl)-piperazine	38.6
1-Cyclohexen-2-yl-4-(2-hydroxyethyl)-2,5-dimethylpiperazine	33.0
1-(2-Hydroxyethyl)-2,5-dimethylpiperazine	69.7
1-Phenyl-4-(2-hydroxyethyl)-2,5-dimethylpiperazine-dihydrochloride	4.1

TABLE VI--Continued

B. p.				Molecular Formula	Molecular Weight	N, %	
°C	mm.	n_D	°C			Calc.	Found
104.0	9.5	1.4985	26.0	$C_{11}H_{19}N$	165.27	8.38	8.34
120.0	16.0	1.5010	20.0	$C_{10}H_{16}NO$	166.24	8.36	8.56
161.5	4.2	1.5215	26.5	$C_{12}H_{22}N_2O$	210.31	13.3	13.1
173.0	6.5	1.5157	27.0	$C_{14}H_{26}N_2O$	238.36	11.8	11.9
121.0	10.0	1.4925	26.0	$C_6H_{18}N_2$	158.24	17.7	17.7
M. p. 235.5-237.5	....	.....	....	$C_{14}H_{22}N_2O$ ·HCl	307.26	9.15	8.84
						Chlorine	
						23.2	23.2
						Carbon	
						54.8	54.6
						Hydrogen	
						7.88	7.85

TABLE VII

COMPARISON OF THE BOILING POINTS OF CYCLOHEXYL, CYCLOHEXENYL, AND PHENYL ALKYLATED AMINES

Alkylated Amine	B. p.					
	Cyclohexyl		Cyclohexenyl		Phenyl	
	°C	mm.	°C	mm.	°C	mm.
NH_2	134	760	137	760.0	184.4	760
NHMe	45-47	20	67	14.0	90.5	20
$N(Me)_2$	60	15	79	34.0	85	20
NHEt	62-65	15	70	15.0	96	20
$N(Et)_2$	85-87	15	60	6.0	92	10
NHPr	...	...	66	6.0	222	760
NHisoPr	...	...	74	24.0	212	760
$N(Pr)_2$	...	...	118	27.0	238	760
NHBu	87-90	12	84	9.5	97	5
$N(Bu)_2$	...	...	84	1.5	149	4
$N(isoBu)_2$	...	...	102	6.0	246	760
NHisoAm	89-93	11	...	.....	126	14
$N(isoAm)_2$	...	...	148	16.0	150	16
NHAm	...	...	95	7.0	130	11
$N(Am)_2$	...	...	106	1.0	285	760
NHHex	...	...	111	6.0	158	28
NHHept	132	16	124	6.5	161	21

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Committee Report

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee and has been approved by all members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Dean

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